AMENDMENTS TO THE DRAWINGS

Drawings 1, 4, and 6-11 were objected to for poor quality. Drawings 1, 6, and 7 are objected to as not labeled separately or properly. Drawings 5, 6, and 12-17 are objected to as not containing lines, numbers and letters that are uniformly thick and well defined, clean, durable and black. Drawings 12 to 17 are objected to as numbers and reference characters are not plain and legible. The replacement sheets attached hereto at tab 1 correct all of the aforementioned objections.

REMARKS

Claims 1 and 17 stand amended to more particularly point out that the claimed model of compact adult bone accounts for the hierarchical structural components of bone including at least microstructure and ultrastructure as well as the viscoelastic properties of these components. Support for this amendment appears in paragraph [0005] describing the morphological/hierarchical classification of adult human bone, and paragraphs [0016] and [0017] providing that the claimed model provides a geometric/material model of hierarchical bone based on the mechanical properties and relative components of osteons, the predominant microstructural component of adult bone. Other amendments are editorial and are made for clarity of expression. The amendments emphasize that the claimed model is not a gross approximation of bone structure, does not broadly assume microstructural uniformity, e.g., of collagen bundles, and does not use assumptions of homogeneity at different orders of bone structure to estimate the interactions of bone with external force. Instead, the claimed model provides a complete model of a compact adult bone by accounting for the first three orders of the hierarchical classification of adult human bone, including bone microstructure and bone ultrastructure, and correlates the components of these orders with their respective viscoelastic properties.

Claims 1-6. 10, 11, 16-23 and 26 stand rejected. Claims 7-9, 12-15, 24 and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants thank the examiner for indicating that some claims are allowable. Applicants respectfully traverse all of the claim rejections.

35 U.S.C. §102(a)--Claims 1, 2, 10, and 20

Claims 1, 2, 10, and 20 stand rejected under 35 U.S.C. §102(a) as anticipated by Crolet, *et al.*, "Compact bone: Numerical simulation of mechanical characteristics," 26 J. BIOMECHANICS 677-687 (1993) ("Crolet"). On page 3 of the Office Action it is noted that "Crolet et al. teaches a model of compact adult bone, wherein the model comprises the viscoelastic properties of at least one type of osteon.

Applicants respectfully traverse this rejection.

Crolet teaches an oversimplified theory of bone macrostructure which presumes there are uniform collagen fibrils per osteon, resulting in an entire osteon that is homogenous and isotropic (not direction dependent), i.e., a simple average. Crolet also assumes that collagen fiber and hydroxyapatite are homogeneous, isotropic, and linearly elastic (p. 679, col. 1, para. 3). Crolet further assumes collagen to be perfectly embedded in hydroxyapatite without lacunae and with a rigid interface (p. 679, col. 1, para. 3).[1] Based upon these assumptions, Crolet calculates the elasticity tensor of one sector, i.e., one lamella, and expands this homogenized estimation to characterize behavior of all lamellar sectors (pp. 679-680). Crolet also uses assumed homogeneous properties to simulate groups of osteons which are not homogeneous (pp. 680-681). This is a poor model because homogeneous groups of osteons cover only a small region of an actual bone. Crolet further does not assemble groups of osteons into a model of macroscopic properties of an entire bone, e.g., a femur. Accordingly, Crolet disregards the dynamic hierarchy of bone structure because it makes unrealistic estimates of structure (e.g., "averaging" osteon structure) and viscoelastic properties (e.g., assuming linear elasticity). The lack of recognition and use of the hierarchical structural and viscoelastic properties limit the Crolet model and is quite different from the invention as claimed.

For example, each osteon in the model of the instant application is built up of regions that are <u>not</u> homogenous and isotropic because the regions include microstructure and ultrastructure correlated with viscoelastic properties of the components of the bone structure. By accounting for the hierarchical bone structure and the viscoelastic properties, the model of the instant application models each osteon non-homogenously, not treating each osteon as uniform. The instant application further assembles groups of osteons into a model of the macroscopic properties of an entire bone. As a result, the focus of the instant application is different than Crolet and results in a

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[1] Later publications show that Crolet's assumptions are incorrect. *See* Ascenzi, M-G., "*A first-estimation of prestress in so-called circularly fibered osteonic lamellae*," 32 J. Biomechanics 935-942, at 941 (1999) (Tab 2) ("Ascenzi 1999"). Ascenzi 1999 discloses a model of a "bright" lamella

different granularity. Accordingly, Crolet does not anticipate claim 1 because it does not account for the hierarchical structural classification of bone including bone microstructure and ultrastructure, and further does not correlate the viscoelastic properties with structure.

Crolet also does not include “the viscoelastic properties of at least one type of osteon” as in claim 1 but instead estimates an entire osteon based purely on theory. Further, static loading, not dynamic loading, is used to evaluate bone characteristics (Crolet, pp. 679, 685). This simplification does not meaningfully account for the viscoelastic properties of bone, particularly for trauma and fracture situations. According to the claimed invention, the viscoelastic behavior of bone under variable or catastrophic stress and strain can be realistically modeled. The application of a constant load, per Crolet, does not achieve this result. *See*, Kotha, W.P. and Guzelsu, N. "*Tensile Damage and its Effects on Cortical Bone*," 36 J. Biomechanics 1683-1689 (2003); and Kotha, S.P. et al, "*Modeling the Tensile Mechanical Behavior of Bone Along the Longitudinal Direction*," 219 J. Theoretical Biol. 269-279 (2002) (both submitted herewith in an Information Disclosure Statement). No viscoelastic properties are realistically accounted for in Crolet, accordingly, Crolet does not anticipate claim 1.

<u>35 U.S.C. §103(a)</u>

1. Crolet, Carter, and Wolfinbarger--Claims 3, 4, 11, and 21

Claims 3, 4, 11, and 21 stand rejected under 35 U.S.C. §103(a) as unpatentable over Crolet in view of Carter, *et al.*, "Mechanical properties and composition of cortical bone," 135 CLIN. ORTHOP. 192-217 (1978) ("Carter") and further in view of U.S. Patent No. 6,293,970 to Wolfinbarger, Jr., *et al.* ("Wolfinbarger"). The Office Action contends that Crolet teaches the model of claim 1 as well as the claimed viscoelastic properties in claim 3, e.g., collagen content, hydroxyapatite content, collagen bundle orientation, and content of porosity fluids. The Office Action further argues that Carter discloses the claimed mechanical properties while Wolfinbarger

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and demonstrates that bright lamella cannot consist entirely of transverse collagen bundles (as in Crolet), but oblique bundles need to be present as well.

discloses mucopolysaccharide, osteocyte, and osteoblast content. Thus, it would allegedly have been obvious to combine Crolet, Carter, and Wolfinbarger to arrive at the presently claimed invention.

Applicants respectfully transverse this rejection.

As noted above, Crolet discloses a mathematical model of bone that assumes an osteon is homogeneous and isotropic. Crolet does not disclose collagen content, hydroxyapatite content, collagen bundle orientation, and content of porosity fluids as the examiner contends, but instead assumes that collagen fiber and the hydroxyapatite are homogeneous, isotropic and linearly elastic (p. 679, col. 1, para. 3) and that collagen is perfectly embedded in hydroxyapatite without lacunae and with a rigid interface (p. 679, col. 1, para. 3). Crolet also does not account for the specific location of biological fluids in bone (p. 685, col. 2, para. 1). Such an over-simplification does not account for the dynamic microstructure and ultrastructure of bone. Crolet then makes groups of osteons which are not homogeneous, however, groups of these osteons cover only a small region of an actual bone (pp. 680-681). At best, Crolet provides a "partial" over-simplified model of bone.

Carter does not cure the deficiencies in Crolet. Carter examines the mechanical properties and composition of bone and concludes that longitudinal osteons are stronger in tension than traversely oriented osteons, and traversely oriented osteons are stronger in compression than longitudinal osteons. However, the disclosure of Carter is based on an oversimplified collagen-apatite distribution model. While Wolfinbarger mentions that bone tissue is comprised of osteoid, e.g., mucopolysaccharies, and minerals, it teaches a plasticized dehydrated or freeze-dried bone product that approximates properties in normal bone. This plasticized bone is a homogenous approximation of the complex and ever-changing structure of bone.

There is no suggestion or motivation to combine the reference teachings to arrive at the model of claims 3, 4, 11, and 21. Both Crolet and Wolfinbarger teach broad assumptions of the structure of bone, and Carter examines one portion of the heterogenous structure. The combination of references does not suggest a model comprising the claimed complex characteristics, e.g.,

“viscoelastic properties” of an osteon, such as "mechanical properties, collagen content, mucopolysaccharide content, hydroxyapatite content, collagen bundle orientation relative to the osteon axis, osteocyte content, osteoblast content, and content of porsity fluids." The combination further does not provide a model that accounts for bone microstructure, bone ultrastructure in connection with the viscoelastic properties. The claimed model is based on observed mechanical properties of osteons which can neither be inferred from macroscopic samples nor derived by purely mathematical models or biochemical tests. The combination of references would at best, teach a model based upon assumptions. Neither Carter nor Wolfinbarger provide information to solve the shortcomings of Crolet.

Accordingly, it would not have been obvious to combine Crolet, Carter, and Wolfinbarger to arrive at claims 3, 4, 11 and 21.

2. Crolet, Carter, Wolfinbarger, and Ascenzi I--Claims 5, 6, 22, and 23

Claims 5, 6, 22, and 23 stand rejected under 35 U.S.C. §103(a) as obvious in view of Crolet, Carter, Wolfinbarger, and Ascenzi, *et al.*, "The torsional properties of single selected osteons," 27 J. BIOMECHANICS 875-884 (1994) ("Ascenzi I"). The Office Action contends that Crolet, Carter and Wolfinbarger teach the model of claim 3, and that Ascenzi I teaches osteon mechanical properties comprising an angle-of-twist as a function of torque, strain rate or time where angle-of twist as a function of torque is derived from tests conducted under monotonic or dynamic loading, e.g., quasi-static torsional loading to rupture. Accordingly, the Office Action concludes that it would have been obvious to modify the model of Crolet with the model of Ascenzi I, in view of Carter and Wolfinbarger to arrive at the presently claimed invention.

Applicants respectfully traverse this rejection.

As noted above, Crolet, Carter, and Wolfinbarger in combination are not sufficient to render claims 3, 4, 11, and 21 obvious. Claims 5 and 22, dependent from claims 3 and 21, respectively, recite mechanical properties, e.g., "angle-of-twist as a function of torque, osteon hydroxyapatite content, strain rate, or time." Claim 6 (dependent from claim 3) recites "angle-of-

twist as a function of torque...derived from tests conducted under monotonic or dynamic loading," and claim 23 (dependent from claim 21) recites "angle-of-twist as a function of torque...determined by quasi-static torsional loading to rupture." The addition of Ascenzi I does not overcome the shortcomings of Crolet, Carter, and Wolfinbarger to arrive at claims 5, 6, 22, and 23. There is no suggestion or motivation in the references to combine the teachings to arrive at the novel claimed model. An assumption that the combination obviates claims 5, 6, 22, and 23 is based upon hindsight reasoning, reached only by examination of the instant application. Accordingly, claims 5, 6, 22, and 23 are not obvious over Crolet, Carter, Wolfinbarger, and Ascenzi I.

3. Crolet and Ascenzi I--Claim 16

Claim 16 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of Ascenzi I. The Office Action contends that while Crolet teaches the model of claim 1, it does not expressly teach the model comprising a Finite Element Model (FEM). The Office Action further contends that Ascenzi I teaches that the mechanical properties of the osteons can be determined by applying finite element analysis. Accordingly, based upon these alleged characterizations, it would have been obvious to combine Crolet and Ascenzi I to arrive at claim 16.

Applicants respectfully traverse this rejection.

As noted above, Crolet discloses a mathematical model of bone that assumes homogenenization of osteons. Crolet then groups osteons to cover only a small region of an actual bone. Furthermore, the FEM in Ascenzi I would not render the claimed model of viscoelastic properties of an osteon including FEM obvious. Instead, the claimed model includes data based upon observation, experimentation, *and* mathematical analysis.

There is no suggestion or motivation in the references to combine the teachings to arrive at the novel claimed model. An assumption that the combination obviates claim 16 is based upon improper hindsight reasoning, reached only by examination of the instant application. Accordingly, claim 16 is not obvious over Crolet and Ascenzi I.

4. Crolet and Carter--Claim 17

Claim 17 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of Carter. The Office Action argues that Crolet discloses a model of viscoelastic properties of longitudinal and alternate osteons and that Carter teaches a method of predicting deformation and fractures of compact adult bone. Accordingly, based upon these alleged characterizations, it would have been obvious to modify the method of Crolet with the method of Carter to arrive at claim 17.

Applicants respectfully traverse this rejection.

As noted above, Crolet discloses a mathematical model of bone that assumes homogenenization of osteons. Crolet then groups osteons to cover only a small region of an actual bone. Carter examines the mechanical properties and composition of bone based upon an over-simplified collagen-apatite distribution model, and concludes that longitudinal osteons are stronger in tension than traversely oriented osteons, and that traversely oriented osteons are stronger in compression than longitudinal osteons. By contrast, the claimed method of predicting deformation and fractures of adult bone comprises using a model of bone wherein the model comprises the viscoelastic properties of longitudinal and alternate osteons.

There is no suggestion or motivation in the references to combine the teachings to arrive at the novel claimed method. An assumption that the combination obviates claim 17 is based upon improper hindsight reasoning, reached only by examination of the instant application. Accordingly, claim 17 is not obvious over Crolet and Carter.

5. Crolet, Carter, and Ascenzi I--Claim 18

Claim 18 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of Carter and further in view of Ascenzi I. The Office Action argues that Crolet and Carter teach the method of claim 17, and that Ascenzi I teaches simulation of fracture propagation by calculating stress distribution as a function of torque applied to the bone. Therefore, based upon these alleged

characterizations, it would have been obvious to modify the method of Crolet and Carter with the method of Ascenzi I to arrive at claim 18.

Applicants respectfully traverse this rejection.

Claim 18 recites a method as in claim 17, wherein the model simulates fracture propagation by calculating stress distribution as a function of torque applied to bone. The combination of Crolet, Carter and Ascenzi I does not render the claimed model of bone obvious because it would be based upon the osteon homogenization theory and incomplete bone characterization of Crolet. Accordingly, a method of predicting deformation using such a model would not have been obvious based upon the combination of prior art teachings that suggest nothing more than a mathematical model and isolated experimentation upon portions of bone.

There is no suggestion or motivation in the references to combine the teachings to arrive at the novel claimed method. An assumption that the combination obviates claim 18 is based upon improper hindsight reasoning, reached only by examination of the instant application. Accordingly, claim 18 is not obvious over Crolet, Carter, and Ascenzi I.

6. Crolet Copeland III, and Agrawal--Claim 19

Claim 19 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of U.S. Patent Nos. 6,333,313 to Copeland III ("Copeland III") and 5,947,893 to Agrawal ("Agrawal"). The Office Action contends that Crolet teaches the model of claim 1, Copeland III teaches a method of identifying the requirements of bone reconstruction, and Agrawal teaches a method of identifying the requirements of prosthesis.

Applicants respectfully traverse this rejection.

Claim 19 of the instant application recites a method of identifying the requirements of bone reconstruction and prosthesis using the model of claim 1. As noted above, Crolet discloses a mathematical model of bone that assumes homogenenization of osteons. Crolet then groups

osteons to cover only a small region of an actual bone. Agrawal discloses a method for incorporating a biodegradable composition onto and into a microporous surface of a metal or joint replacement prosthesis (see claim 1). Copeland III discloses use of oxytocin alone or in combination with other drugs to treat bone diseases (see Abstract). Crolet, Copeland III and Agrawal in combination do not render claim 19 obvious because none of the references teach or suggest the inventive model, and further do not suggest identification of the requirements of bone reconstruction and prosthesis using such a model. Crolet, a mathematical simulation, in combination with Copeland III, a method of treatment using oxytocin, and Agrawal, a method for easing prosthesis to tissue adhesion as well as drug delivery, in no way teach the claimed method.

An assumption that the combination obviates claim 19 is based upon improper hindsight reasoning, reached only by examination of the instant application. Accordingly, claim 19 is not obvious over Crolet, Copeland III, and Agrawal.

7. Crolet, Carter, Wolfinbarger, Hamamoto, and Ascenzi II--Claim 26

Claim 26 stands rejected under 35 U.S.C. §103(a) as obvious over Crolet in view of Carter, Wolfinbarger, U.S. Patent No. 5, 732,469 to Hamamoto ("Hamamoto") and Ascenzi et al, "X-ray diffraction on cyclically loaded osteons," 62 CALCIF. TISSUE INT. 266-273 (1997) ("Ascenzi II"). The Office Action argues that Crolet, Carter, and Wolfinbarger teach the method of claim 21, Hamamoto teaches collagen-bundle direction related to osteon axis is determined by circularly polarizing light microscopy or confocal microscopy, and Ascenzi II teaches collagen-bundle direction related to osteon axis is determined by X-ray diffraction. Accordingly, based upon these alleged characterizations, it would be obvious to one of ordinary skill in the art to modify the method of Crolet with the method of Ascenzi II to arrive at claimed method 26.

Applicants respectfully traverse this rejection.

Claim 26 recites a method of preparing a model of the viscoelastic properties of bone, wherein the collagen-bundle direction related to osteon axis is determined by circularly polarizing light microscopy, confocal microscopy, or X-ray diffraction.

As noted above, Crolet discloses a mathematical model of bone that assumes homogenenization of osteons and then groups osteons to cover only a small region of an actual bone. Carter examines the mechanical properties and composition of bone based upon an over-simplified collagen-apatite distribution model, and concludes that longitudinal osteons are stronger in tension than traversely oriented osteons, and that traversely oriented osteons are stronger in compression than longitudinal osteons. While Wolfinbarger mentiones that bone tissue is comprised of osteoid, e.g., mucopolysaccharies, and minerals, it teaches a plasticized dehydrated or freeze-dried bone product that approximates properties in normal bone. This plasticized bone is a homogenous approximation of the complex and ever-changing structure of bone.

Hamamoto discloses a porous lamination component of metal thin sheets for composing a prosthesis for replacement of hard tissues of human bones and joints (see Hamamoto Abstract). And Ascenzi II presents the results of an investigation of isolated osteons by X-ray diffraction (see Ascenzi II Abstract).

The cited combination does not suggest the claimed method using a realistic bone model, wherein one portion of the model, collagen-bundle direction, is determined by microscopy techniques or X-ray diffraction. Instead, the combination of references would, at best, suggest a mathematical model assuming that bone structure is homogenous, in combination with experimental studies on components of bone and bone prosthesis products. None of the references would motivate one having skill in the art to arrive at the novel method without hindsight examination of the instant application. Accordingly, claim 26 is not obvious over Crolet, Carter, Wolfinbarger, Hamamoto, and Ascenzi II.

In view of the above remarks, applicants believe the pending application is in condition for allowance.

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Respectfully submitted,

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Attachments